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COMPARATIVE EFFECT OF AZILSARTAN, OLMESARTAN AND TELMISARTAN IN INDIAN ADULT HYPERTENSION PATIENTS

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ABSTRACT

BACKGROUND

Angiotensin II Receptor Blockers (ARBs) are the newest class of approved antihypertensive agents and important drugs in the treatment of hypertension by applying their primary antihypertensive action and interrupting the renin-angiotensin system, in adult patients. Objectives: Using a randomized, double-blind trial in patients with hypertension, the efficacy of Azilsartan (40 mg once a day), Olmesartan (20 mg once a day), and telmisartan (40 mg once a day) were a compared1 hour before the meal., which were assessed in patients with a cuff Diastolic Blood Pressure (DBP) between 100 and 115 mm Hg and a mean daytime DBP between 90 and 120 mm Hg measured by Ambulatory Blood Pressure Monitoring (ABMP).

MATERIALS AND METHODS

Both cuffs and ambulatory blood pressures were monitored at baseline and after 16 weeks. The study participants comprised adults and approximately 66% were male. The mean baseline diastolic blood pressure (DBP) and systolic blood pressure (SBP) was approximately 102 and 154 mmHg, respectively, among all groups. With Azilsartan the reduction in sitting cuffed DBP (13.2 mm Hg), which is the primary efficacy variable of this study, was significantly greater compared to olmesartan and telmisartan (9.9 and 7.9 mm Hg, respectively). However, with all ARBs, the reductions in cuff SBP ranged from 8.6 to 13.6 mm Hg, which were not significantly different. The reduction in mean 24-hour DBP with Azilsartan (8.7 mm Hg) was significantly greater compared to Olmesartan and Telmisartan (7.6 and 6.2 mmHg, respectively, p = 0.087). The reduction in mean 24-hour SBP with Azilsartan (12.6 mm Hg) was significantly greater compared to Olmesartan and Telmisartan (9.1 and 8.2 mmHg, respectively), though all the drugs were well tolerated.

RESULTS

Of the 224 patients screened, 135 patients were eligible for the study participants in the trial and were put on azilsartan (n =45), olmesartan (n = 45),and telmisartan(n = 45) on a random basis. Failure to meet the blood pressure entry criteria (70%) and patient request (9%) were the main reasons for the discontinuation even before randomization. In each group, the percentage of patients who completed the entire 16 weeks of the study were 91.0%, 92.3% and 95.4% for azilsartan, olmesartan andtelmisartan, respectively. The study showed that the differences in cuff blood pressure reduction after treatment with azilsartan, olmesartan and telmisartan were evident within 4 weeks. Azilsartan-treated group of patients had the mean DBP decreased by 11.3 mm Hg, whereas the group that was treated with olmesartan drug showed a mean DBP decrease of 8.1 mm Hg, and telmisartan-treated patients showed a common decrease of 9.0 mm Hg.

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CONCLUSIONS

An initial dose of 40 mg Azilsartan is more effective than the starting doses of the other drugs like olmesartan and telmisartan in reducing cuff DBP in patients with essential hypertension in Indian adult patients.

KEYWORDS: Essential Hypertension, Azilsartan, Olmesartan & Telmisartan

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INTRODUCTION

Angiotensin II Receptor Blockers (ARBs) also known as angiotensin II receptor antagonists, AT, receptor antagonists or sartans are the latest class of approved Antihypertensive agents and also the important class of drugs used to apply their primary Antihypertensive action by modulating the renin-angiotensin -aldosterone system. By selective blockade of the angiotensin II type 1 (AT1) receptor, ARBs prevent the hypertensive effects of angiotensin II. [1]

The latest angiotensin I receptor antagonist AT1, azilsartan, was discovered by modifying the tetrazole ring in candesartan, olmesartan, losartan, telmisartan, and valsartan. In clinical list worldwide, Azilsartan is the 8th ARB. In 2011, a prodrug of azilsartan, Azilsartanmedoxomil, was approved by USFDA for HTN treatment. In 2012, it was approved in Japan too. An Azilsartanmedoxomil and azilsartanproved to have greater Antihypertensive effects than other ARBs. Azilsartanmedoxomil, also known by the US accepted the name of azilsartankamedoxomil, is chemically described as (5-methyl-2-oxo-1, 3-dioxol-4-yl) methyl 2-ethoxy-1-{[2'-(5-oxadiazole-3-yl) biphenyl l-4-yl] methyl}-1H-benzimidazole-7-carboxylate monopotassium salt. Azilsartan is structurally similar to candesartan except that it bears a 5-oxo-1, 2, 4-oxadiazole moiety in place of the tetrazole ring. Due to this chemical alteration,there is increased lipophilicity of Azilsartanmedoxomil and improved oral bioavailability.[2,3]

In a systematic survey of substituted imidazole-5-carboxylic acids, a newer ARB called Olmesartan was discovered. It is a prodrug whose administration causes rapid and complete de-esterification in the gut, forming its active form in a reaction that is independent of cytochrome P-450. Olmesartan, an active metabolite is a potent and selective AT1 receptor antagonist with no antagonist activity. [4,5]

Telmisartan possesses the biphenyl-tetrazole and imadazole group common to all ARBs which highly prefers angiotensin II type 1 receptor (AT1), stopping the deleterious effects of angiotensin II, which include vasoconstriction, activation of the protein kinase C, and release of catecholamines from the adrenal medulla, aldosterone secretion.[6] Olmesartan has an elimination half-life of 12-18 hours, a value that is comparable to the longest half-lives of ARBs presently in clinical use. According to a dose-ranging study, olmesartan is effective once per day for the HTN treatment, and this is based on ambulatory blood pressure measurements and to have a safety profile similar to that of placebo.[7,8]

Previous studies have compared the Antihypertensive efficacy of ARBs on the basis of cuff blood pressure change, but they were all largely against losartan only.[9] Early in the course of atherosclerosis, endothelial dysfunction occurs in response to cardiovascular risk factors and contributes to the morbidity of the coronary disease.[10] In animal models, angiotensin-converting enzyme inhibition has a favorable effect on the endothelial function.[11] Studies reveal that the mediator responsible for the beneficial effects of ACE inhibition on endothelial function and atherosclerosis development is bradykinin. However, in some studies, angiotensin II blockers, the agents that have no effect on bradykinin,

have demonstrated the beneficial vascular effects comparable to ACE inhibitors.

MATERIALS AND METHODS

Patients in the age group of 18 years and above both male and female with essential hypertension were considered as eligible for participation in this study and patients with an average cuff Diastolic Blood Pressure (DBP) of >100 and < 115 mmHg and a mean daytime DBP of > 90 and < 120 mm Hg was measured by an ABPM device after successfully completing a period of 4-week placebo run. Women of child-bearing age, who were not using any kind of pregnancy control measures, and who were lactating women were excluded from the study, including patients with cardiovascular disease within the past 6 months, patients with serious disorder that limits the ability of the patient to participate in the trial and also patients with secondary hypertension were excluded from the study. Other than the drugs used in the study no other antihypertensive medications were allowed during the placebo run and active treatment phases of this trial. In the first phase of the study, the patients were required to stop taking such medications at least 24 hours prior to receiving the first dose of placebo run. Special permission was sought from the Institutional Ethics Committee for this randomized, double-blind, parallel group, clinical trial. With the help of random number table, randomization was done by a statistician. This study was divided into three phases: initial screening, 4-week single-blind placebo run and 8-week double-blind active treatment. During the first phase of screening, patients had to sign a consent agreement and their medical history was checked. As part of the study, patients had to undergo a physical examination, 12-lead electrocardiography and also laboratory tests. Blood and urine samples were collected and tested after the patients fasted for a minimum of 8 hours. A mercury sphygmomanometer is used to measure the sitting cuff blood pressure and the patients were advised to rest for a minimum of 5 minutes before checking their first cuff blood pressure. Three separate readings were taken at an interval 1 minute. During the measurement of the second blood pressure reading, the pulse rate was also taken.

In the 4-week single-blind, placebo run-in phase of the study, only those patients who met the entry criteria were only eligible. At the end of each week of the run-in period (designated visits 1-4), blood pressure and heart rate were recorded. The daily average cuff DBP at both visits 3 and 4 was ≥ 100 mg Hg and ≤ 115 mm Hg, and the daily average was ≤10 mm Hg, the patient was considered eligible for ABPM. Ineligible patients, ABPM was started immediately after the cuff blood pressure measurement during the 4th visit and was continued for 24 hours. Patients with a mean daytime DBP of ≥90 mm Hg and < 120 mm Hg by ABPM were eligible for treatment randomization.

The study shows that the patients entering the active treatment phase were randomly assigned to receive daily a single dose of one of the following ARBs: azilsartan 40 mg, olmesartan 20 mg, and telmisartan 40 mg. Only recommended dosages were provided. The starting recommended dose consisted of all drugs taken at breakfast, which were categorized as identical capsules matching the placebo capsules administered during the run-in phase of the study. But on examination days, the medication was not taken until blood pressure had been measured. After commencing treatment and before taking their daily medication dose, patients were to visit the clinic 4, 8 and 16weeks. The sitting cuff blood pressure and the heart rate were measured in triplicate at each visit, reaching compliance by assessing the pill count, and patients were queried for adverse events. Only at week 16, the ABPM was measured. If the average sitting cufedSystolic Blood Pressure (SBP) was 200 mm Hg or if the mean daytime or average sitting cuff DBP was ≥ 120 mm Hg at any visit, the patient was treated with appropriate Antihypertensive medication but removed from the study.

Acceptance Criteria for ABPM Data

Throughout the 24 hours period, the ABPM devices were programmed to record the blood pressure every 15 minutes. The data collected using ABPM were accepted only if medication administration occurred between 6.30 a.m. and 9.30 a.m. and also the data were collected for a minimum period of 24 hours after drug administration, thereby considering at least one reading valid. During the 24-hour collection period, if there were 6 or more nonconsecutive hours with no readings or 2 or more consecutive hours with no readings, the data was rejected.

Statistical Design

The typical curve representation of circadian blood pressure variation was followed the supreme objective of this study was to assess the comparative efficacy of azilsartan, olmesartan, telmisartan in terms of controlling the high blood pressure levels. The primary efficacy variable was the change in sitting cuff DBP from baseline to the 16-week visit in the active treatment phase. The parameters of the secondary efficacy variables were changed in sitting cuff DBP from baseline to week 4 and 8 visits, change in sitting cuff SBP from baseline to week 4, 6 and 16 visits and change in mean 24-hour ambulatory DBP and SBP from baseline to week 16. After 16 weeks' treatment, the duration and consistency of 24-hour blood pressure control were estimated by determining the DBP and SBP trough to peak ratio, which is defined as the ratio of the lowest value of the fitted curve and the highest value of the fitted curve. This ratio was calculated by determining the difference between the baseline and week 16 measurements for each hour of ABPM recording. The typical curve representation of circadian blood pressure variation was followed. From each treatment group, the plots of the hourly mean values were fitted using a seven-term Fourier series.

The decrease in cuff sitting DBP during treatment with Azilsartan would be 4.4, 3.8 and 3.0 mmHg greater compared with the decreases during treatment with olmesartan and telmisartan, respectively, thereby arriving at the required sample size of the treatment groups. Thus the leading to the assumption that with an overall one-sided significance level of 0.05 and 90% power, 135 patients per treatment group were required for this trial. The intention-to-treat population is those having received at least one dose of study medication after randomization and for whom baseline and one post baseline measurements were available. In instances when a patient discontinues treatment before the study end, the last measurement was considered for analysis, prior to removal from the trial. Baseline demographic characteristics were compared among treatment groups. Categorical variables were determined by chi-square test and continuous variables with Analysis of Variance (ANOVA) with the treatment used as a factor and paired t -tests were used to determine the changes in blood pressure within each treatment group during the study. A probability (p) of 0.05 was considered significant.

An analysis of covariance (ANCOVA) model was used to determine the differences among treatment groups in the primary efficacy variable (change in cuff DBP over the 16 weeks of treatment), with baseline as the covariate and treatment and center as factors. To compare the least square means computed from ANCOVA models, one-sided tests were used. A multiple-test procedure was used was used to adjust the p values, thereby ensuring that the overall significance level remained at 5%. For all other comparisons of cuff blood pressure and for ambulatory blood pressure comparisons, a similar ANCOVA model was used.

Analysis of Covariance (ANCOVA) model was once again used to determine the differences among treatment groups in the primary efficacy variable (change in cuff DBP over the 16 weeks of treatment), with an with baseline as the covariate and treatment and center as factors. From ANCOVA models, the least squared means were computed which in

turn was used to one-sided tests. The p values were adjusted with a multiple-test procedure, ensuring the overall significance level at 5%. For comparisons of cuff blood pressure and ambulatory blood pressure, the ANCOVA model was used.

Safety

To understand the seriousness and its relation to the study, it was necessary to record all adverse events reported by patients or observed by investigators, thereby assessing the clinical significance. Adverse event data are presented for the period of active treatment only and all randomized patients are included. For differences among treatment groups, Fisher's exact test was used to analyze the clinical and laboratory adverse event data. During the physical examination, clinical significant changes that occurred between screening and the end of the study findings were also recorded.

RESULTS

Of the 224 patients, 135 entered the treatment phase of the study and were randomized to Azilsartan (n = 45), olmesartan (n = 45), and telmisartan (n = 45). Failure to meet the blood pressure entry criteria (68%) and patient request (10%) are the most common reasons for discontinuation prior to randomization. In all, 91.0%, 92.3% and 95.4% patients completed the entire 16 weeks of the study for Azilsartan, olmesartan and telmisartan, respectively.

Baseline Demographics

With regard to the demographics of the different treatment groups, no significant differences were observed. The mean age of all groups was approximately 50 years with 66% male. In all treatment groups, the baseline DBP was approximately 102 mmHg and the baseline SBP approximately 154mm Hg.

Cuff Blood Pressure and Heart Rate

Both cuff DBP and SBP showed a significant decrease after the treatment with ARBs, from baseline to after 16 weeks of treatment ($p < 0.001$ for both groups). The cuff DBP reduction after treatment with Azilsartan (13.2 mm Hg) was significantly greater compared with olmesartan (9.9 mm Hg; $p = 0.0002$) and telmisartan (7.9 mm Hg; $p < 0.0001$). A mean reduction in SBP of 12.6 mmHg was observed with Azilsartanthera by over the 16-week treatment period. Over the same period, the mean SBP reductions of 9.5 and 11.0 mmHg, respectively, were observed in patients treated with olmesartan and telmisartan, which were not statistically significant at 16 weeks.

Table 1: Baseline Demographic Characteristics and Blood Pressure of Patients in the Intent-to-Treat Population

	AZILSARTAN	OLMESARTAN	TELMISARTAN
NO.	45	45	45
Age (year)	52.3 ± 8.75	51.5 ± 8.40	52.6 ± 9.52
Gender%			
Male	66.8	61.5	56.6
Female	32.9	37.7	42.5
Baseline Blood Pressure			
Cuff DBP	102 ± 3.2	102 ± 3.5	102 ± 3.2
Cuff SBP	154 ± 13.2	154 ± 10.5	154 ± 11.5
All values are means ± SD			

Within 4 weeks it was clear that there was a difference in cuff blood pressure reduction after treatment with Azilsartan and each of the comparison drugs (Table 2). In the Azilsartan-treated group, the mean DBP decreased by 10.7

mmHg, while the Olmesartan-treated group had a mean decrease of 7.6 mmHg and in the telmisartan-treated group, the decrease was 9.0 mmHg. Among the treatment groups, similar differences in DBP reduction were evident in the week 8 data (Table 2). For all comparisons at both 4 and 8 weeks, there were significant differences in DBP response between Azilsartan and the comparison drugs. Compared to three drugs, azilsartan was significantly effective in reducing SBP after 4 weeks, but not at 8 weeks of treatment (Table 2). In the Azilsartan-treated group, at 4 weeks, the mean SBP was reduced by 13.0 mmHg compared with 8.9 mmHg in the olmesartan group (p = 0.001) and 9.2 mmHg in the telmisartan group (p = 0.003). At week 8, the changes in SBP were not significantly different in the olmesartan-treated group and the comparison drugs' groups. There was no significant change in heart rate in any of the ARBs used in this study.

Table 2: Change in Cuff DBP and SBP after 4 and 8 Weeks of Treatment

	Azilsartan	**Olmesartan**	**Telmisartan**
4 Weeks			
Δ DBP	-10.7	**-7.6†**	-9.0*
Δ SBP	-13.0	**-8.9****	-9.2**
8 Weeks			
Δ DBP	-11.4*	**-8.9†**	-9.7*
Δ SBP	-13.4	**-11.4**	-10.6

After 4 and 8 weeks of treatment with olmesartan, Azilsartan, and Telmisartan, the least squares mean change at baseline for cuff Diastolic Blood Pressure (DBP) and Systolic Blood Pressure (SBP) was *p = 0.05 vs. olmesartan; **p = 0.005 vs. olmesartan; †p = 0.0005 vs. olmesartan.

Ambulatory Blood Pressure Monitoring

Compared with olmesartan and telmisartan (6.2 and 5.7 mm Hg, respectively), the mean reduction in 24-hour DBP with Azilsartan (8.4 mm Hg) was significantly greater.

In the ambulatory SBP data, a similar difference pattern was evident. After 16 weeks, Azilsartan reduced the mean 24-hour SBP by 12.6 mmHg, which was significantly greater than that achieved by olmesartan and telmisartan (9.0 and 8.1 mmHg, respectively). Table III shows the changes in mean daytime and nighttime DBP and SBP as measured by ABPM after 16 weeks of treatment with the various ARBs. For purposes of these measurements, 8:00 a.m. to 7:59 p.m. was considered daytime and 8:00 p.m. to 7:59 a.m. as nighttime. Both mean daytime DBP and SBP (10.2 and 14.7 mmHg, respectively) showed the reduction after the treatment with Azilsartan for 16 weeks, which was significantly larger compared to those after treatment with olmesartan and telmisartan.

Table 3: Change in Mean Daytime and Night Time ABPM, DBP, and SBP After 8 Weeks of Treatment with Losartaazilsartan, Olmesartan, Telmisartan

	Azilsartan	**Olmesartan**	**Telmisartan**
Day			
Δ DBP	-10.2	-7.2**	-7.0†
Δ SBP	-14.7	-10.9**	-10.2**
Night			
Δ DBP	-6.8	-5.2	-4.2**
Δ SBP	-10.3	-7.3*	-6.1**

ABPM = ambulatory blood pressure monitoring; DBP = diastolic blood pressure; SBP = systolic blood pressure; *p = 0.05 vs. Azilsartan; **p = 0.005 vs. Azilsartan; †p = 0.0005 vs. Azilsartan.

In this study, compared to the daytime, all the ARBs showed less effect on blood pressure during the night. The drop in mean nighttime DBP with Azilsartan treatment (6.8 mmHg) was statistically greater than the nighttime DBP reduction with telmisartan and olmesartan. After 16 weeks of Azilsartan, the reduction from baseline in nighttime SBP (10.3 mmHg) was significantly greater than those with olmesartan (7.3 mmHg) and telmisartan (6.1 mmHg), which was similar to the drop in nighttime SBP [12].

Trough to Peak Ratios

By determining the systolic and diastolic trough-to-peak ratio, the stability of blood pressure was also assessed for each treatment during the 24-hour between-dose period. For SBP, this ratio was highest for Azilsartan (0.69). Olmesartan, telmisartan achieved SBP trough-to-peak ratios of 0.64, 0.55 and 0.62, respectively [AQ: Please check the sentence " Olmesartan, telmisartan achieved SBP..." for clarity and correctness as for two drugs 3 values are provided.]. For DBP, the trough to peak ratios of Azilsartan and olmesartan were similar (0.68 and 0.69, respectively) and higher than those of telmisartan (0.48).. The trough to peak ratios of the four treatment groups was not compared statistically.

Safety

Among the three treatment groups, the overall incidence of adverse events was comparable. At least one clinical adverse event was experienced by 30.6% (n = 45) of the patients treated with Azilsartan, comparing to 32.0% (n = 48) of the olmesartan group, 44.8% (n = 65) of the telmisartan group and 35.6% (n = 52) (Table IV) [AQ: This sentence " At least one clinical adverse event was experienced by 30.6% (n = 45) of the..." seems incomplete. Please check and edit as necessary.]. The most common complaints comprised upper respiratory infection, headache, fatigue, back pain, and dizziness. After randomization (Azilsartan, n = 1; olmesartan, n = 1; telmisartan n = 2) serious adverse events were reported in four patients, which according to the investigator were not related to the study drugs. [13]

During the active treatment period, adverse events were observed in 21 randomized patients. Of these patients, eight received Azilsartan (5.4%), five olmesartan (3.3%), and five telmisartan (3.4%). In the overall incidence of laboratory adverse events or in the incidence of adverse events within any body system, No significant differences were observed among groups.8 four patients (two olmesartan and two telmisartan) showed elevations of alanine aminotransferase or aspartate aminotransferase. Prior to treatment, one showed elevated levels of alanine aminotransferase and γ- glutamyltransferase; at the end of treatment the elevation levels decreased in two patients; and one patient the follow-up levels were not tested. Therefore, it the elevations was not considered significant. After randomization, due to clinical or laboratory adverse events (Azilsartan, n = 2; telmisartan n = 4), six patients discontinued the study [AQ: In the sentence " After randomization, due to clinical or laboratory adverse events..." "seven" has been changed as "six." Please approve.].

Table 4: Adverse Events During the Active Treatment Period

	Azilsartan	Olmesartan	Telmisartan
Patients with ≥ 1 AE During Active Treatment			
Total AEs	44 (30.6)	47 (32.0)	66 (44.8)
Drug-related AEs	11 (8.2)	13 (9.2)	12 (9.0)
Serious AEs (Total	1 (0.7)	1 (0.7)	2 (1.3)
Severe AEs (Total)	4 (2.7	2 (1.3)	3 (2.1)
Total AES in ≥ 2% of Patients in any Treatment Group			
URT Infection	4 (2.7)	4 (2.7)	12 (8.3)
Headache	7 (4.8)	6 (4.0)	6 (4.1)

Table 4: Contd.,			
Fatigue	3 (2.0)	5 (3.3)	3 (2.1)
Back pain	1 (0.7)	5 (3.3)	3 (2.1)
Dizziness	2 (1.4)	1 (0.7)	2 (1.4)
Diarrhoea	2 (1.4)	1 (0.7)	1 (0.7)
Arthralgia	1 (0.7)	3 (2.0)	3 (2.1)
Coughing	3 (2.0)	1 (0.7)	2 (1.4)
Pharyngitis	0 (0.0)	4 (2.7)	1 (0.7)
Influenza-like Symptoms	1 (0.7)	0 (0.0)	1 (0.7)
Myalgia	0 (0.0)	1 (0.7)	4 (2.8)
Peripheral Oedema	1 (0.7)	0 (0.0)	3 (2.1)

DISCUSSIONS

Compared to treatment with starting doses of olmesartan and telmisartan, treatment with Azilsartan results in a significant reduction in cuff DBP, whose superior efficacy was evident in 4 weeks after treatment initiation and was maintained for the duration of the trial [14].

Similar to the change in DBP, the Azilsartan-induced reduction in SBP was rapid at onset. After 4 weeks, Azilsartan-treated patient experienced a mean reduction of 13.0 mmHg in cuff SBP. Mean reductions in the three groups at 4 weeks, but not at 8 weeks, were significantly lower, ranging from 8.9 mmHg (olmesartan) to 10.8 mmHg telmisartan. The efficacy of Azilsartan was maintained at 8 and 16 weeks (reductions of 13.4 and 11.3 mmHg, respectively), though the comparison between olmesartan and telmisartan did not achieve statistical significance at these time periods.[15] Its relatively long half-life (12-18 hours) can be related to the greater efficacy of Azilsartan in reducing trough cuff DBP.[16]

Blood Pressure Differences and Outcome

Data suggest that the small differences sustained over time in DBP reduction between Azilsartan and the other drugs (approximately 2-4 mmHg) may be associated with reductions in cardiovascular risk events. MacMahon et al, through a comprehensive overview of nine prospective observational studies involving 420,000 individuals, concluded that a reduction in DBP of 5 mmHg is associated with reductions of at least 21% in the incidence of coronary heart disease and 34% in the incidence of stroke. According to the Hypertension Optimal Treatment (HOT) trial, there were 28% fewer myocardial infarctions in the treatment group with a target DBP of 80 mmHg compared to the group with a target DBP of 90 mmHg, though the actual difference in mean DBP achieved by these two groups was only 4.1 mmHg. A similarly strong association between the risk of adverse cardiovascular events and both DBP and SBP has also been demonstrated in patients with diabetes. These observations suggest significant differences in DBP reduction with Azilsartan and olmesartan compared to the other ARBs used in the present study may be of clinical value. As with DBP, elevations in SBP lead to increased risk of coronary heart disease, stroke, myocardial infarction, occlusive peripheral arterial disease and congestive heart failure.[17,18]

Several studies quantified the outcomes of adverse cardiovascular risks associated with elevated SBP. According to Kannel, men with SBP of 140 - 159 mmHg had 50% - 75% greater risk of cardiovascular disease than men with SBP of 120 - 139 mmHg. These observations suggest that the magnitude ARB-induced reductions in cuff SBP in the present study are of clinical significance [19].

Trough-to-Peak Ratio

The trough-to-peak ratio is an important parameter to measure the antihypertensive efficacy consistency of a drug during the entire dosing interval because increased blood pressure variability is associated with increased risk of end-organ damage in hypertensive patients [20]. An optimal antihypertensive formulation should provide 24-hour efficacy with a once-daily dose with at least 50% of the peak effect remaining after 24 hours. Lower ratios may reflect excessive and potentially detrimental decreases in blood pressure at peak, poor control of hypertension at the trough or excessive variability of pharmacologic effect, which is of therapeutic importance especially when patients miss a medication dose. All the agents assessed in this study had trough to peak ratios well above 0.5for both DBP and SBP.

Safety

With regard to the incidence of clinical or laboratory adverse events, no differences were observed among the treatment groups, with rare severe adverse events. Among all groups, the total adverse event rate (which ranged from 31% for Azilsartanto 45% for telmisartan) was similar.[21] A headache being one of the most common adverse events among hypertensive patients, and lowering elevated blood pressure reduces the incidence of a headache.

CONCLUSIONS

According to the study's finding the reduction in cuff DBP resulting from 8 weeks of treatment with Azilsartan is was greater than that seen following treatment with olmesartan and telmisartan. Azilsartanalso demonstrated a reduction in cuff SBP, which was greater than olmesartan and telmisartan. The observation that small differences in both DBP, and SBP are associated with substantial reductions in the incidence of major cardiovascular risk events, suggesting that small differences in blood pressure reduction between ARBs may have long-term effects.

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